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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Addendum to 2-year Rat Chronic/Oncogenicity Study With Dowco 233- Evaluation of additional histopathology data submitted by Dow. PP #1F2508; Caswell #822I

TO: Robert Taylor (25)
Registration Division (TS-767)

FROM: D. Stephen Saunders Jr., Ph.D.
Toxicologist, Section V
Toxicology Branch/HED (TS-769)

D. Stephen Saunders Jr.
5-31-84

THRU: Laurence D. Chitlik, DABT
Head, Section V
Toxicology Branch/HED (TS-769)
and
William L. Burnam, Chief
Toxicology Branch/HED

LDC 5/31/84
WLB 6/4/84

I have reviewed the addendum submitted by Dow Chemical Co. containing additional histopathology data in support of the registration of Dowco 233 (Triclopyr). There were numerous tissues from the control and high dose groups which were not examined microscopically from a sufficient number of animals to allow for a valid assessment of the chronic toxicity of this compound. Therefore, the major deficiency identified by Toxicology Branch reviewers (W. Teeters and L. Chitlik) in the IBT validation report, specifically the relative lack of histopathologic data, has not been corrected by the submission of the addendum. This study remains classified as Supplementary data. Table 1 documents tissues and/or potential target organs which were examined in only a relatively small percentage of animals.

The additional statistics package submitted by the registrant (5-14-84) provides no new information. The package documents the statistical significance ($p<0.05$ by Fisher's Exact Probability test) of the histopathological findings noted in this study, i.e. increases in adrenal cortical vacuolation, chronic respiratory disease and lung vascular mineralization in males, and a decrease in adrenal medullary cell hyperplasia in females. The position of Toxicology Branch is that the sample size for many tissues (i.e. the actual number of tissues examined) from the high dose group is too small to assure that no compound-related effects exist for those tissues. Therefore, the scientific validity of statistical assessments on such small sample sizes is questionable.

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For example, the statistically significant increase in adrenal cortical vacuolation was noted in males even though only 36 and 40% of tissues from control and high dose animals, respectively, were examined. The registrant maintains that this effect is a "very common aging change...of no toxicological significance". Had a larger sample of tissues been examined, particularly from the "younger" animals that died on test, this claim would be easier to substantiate. Adrenals from the intermediate dose groups were not examined, apparently on the assumption that these changes were not treatment-related, in contrast to the study protocol which stated that "any significant tissue or organ change at the high dose level would also be examined at the lower levels". Statistically significant effects may have been noted in other tissues from the high dose group had an adequate sample of tissues been available for examination.

We presented our views on the status of this study to representatives of Dow Chemical Corp. in the meeting of 5-14-84, which you attended. While we agree that Dow has made a "good faith" effort to obtain the missing tissues requested in order to upgrade this study, the unfortunate fact is that they have been unable to do so. Their other comments regarding target organ effects and pharmacokinetic considerations really do not pertain to our assessment of this study. We agree that this study provides some useful information, and for this reason it was classified as Supplementary rather than Invalid.

Table 1 (appended) reflects the limited histopathological data available for a large number of important tissues in this study.

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Table 1. Percentage of Tissues Examined Microscopically[a]

	Dose (mg/kg)							
	0		3		10		30	
Tissue	M	F	M	F	M	F	M	F
Brain	36	46	0	0	0	0	40	36
Spinal cord	38	46	0	0	0	0	40	36
Bone/Marrow	36	46	0	0	0	0	36	40
Pituitary	36	44	10	22	10	36	40	36
Stomach	36	46	0	0	0	0	40	40
Sm. intestine	34	23	0	0	0	0	40	40
Colon	32	48	0	0	2	0	40	38
Mesenteric Lymph node	34	42	2	0	2	0	42	40
Prostate	36	-	2	-	0	-	40	-
Urinary bladder	36	56	0	0	0	0	40	46
Mammary	0	38	2	28	6	22	6	36
Thyroid	74	62	0	0	0	0	72	80
Thymus	64	52	0	0	0	0	64	62
adrenal*	36	46	0	12	2	14	40	44

[a]Percentages calculated by reviewer from data supplied in addendum.

*significant increase ($p < 0.05$) in pathological findings noted in high dose group.

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